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  *         U. S.   P A T E N T   T E X T   F I L E                       *
  *                                                                       *
  *  THE WEEKLY PATENT TEXT AND IMAGE DATA IS CURRENT                     *
  *  THROUGH May 18 1999.                                                 *
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=> s packag? cell? and viral vector? and retrovir?

        189546 PACKAG?
        407138 CELL?
           520 PACKAG? CELL?
                 (PACKAG?(W)CELL?)
         18354 VIRAL
         77448 VECTOR?
          1890 VIRAL VECTOR?
                 (VIRAL(W)VECTOR?)
          6076 RETROVIR?
L1         292 PACKAG? CELL? AND VIRAL VECTOR? AND RETROVIR?

=> s l1 and integrat?

        311451 INTEGRAT?
L2         208 L1 AND INTEGRAT?

=> s l2 and pseudotyp?

            88 PSEUDOTYP?
L3          34 L2 AND PSEUDOTYP?

=> d l3,1-34,cit
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1. 5,888,502, Mar. 30, 1999, Recombinant **retroviruses**; Harry E. Guber, et al., 424/93.21, 93.2; 435/320.1, 372.3 [IMAGE AVAILABLE]

2. 5,883,081, Mar. 16, 1999, Isolation of novel HIV-2 proviruses; Gunter Kraus, et al., 514/44; 424/160.1; 435/69.1, 320.1; 530/388.35; 536/23.1 [IMAGE AVAILABLE]

3. 5,879,933, Mar. 9, 1999, Mammalian Retrotransposons; Clague P. Hodgson, 435/320.1, 325 [IMAGE AVAILABLE]

4. 5,877,010, Mar. 2, 1999, Thymidine kinase mutants; Lawrence A. Loeb, et al., 435/320.1, 243, 325; 536/23.2, 23.5, 23.72, 24.1 [IMAGE AVAILABLE]

5. 5,858,771, Jan. 12, 1999, Products and methods for controlling the suppression of the neoplastic phenotype; Wen-Hwa Lee, et al., 435/320.1, 69.1, 458; 536/23.1 [IMAGE AVAILABLE]

6. 5,856,185, Jan. 5, 1999, Method for making reflection defective **retroviral** vectors for infecting human cells; Harry E. Gruber, et al., 435/372, 350, 357, 363, 366, 369; 536/23.4, 23.72 [IMAGE AVAILABLE]

7. 5,851,529, Dec. 2[redacted]1998, Recombinant **retroviruses**[redacted]arry E. Guber, et al., 424/188.1, 93.2, 277.1 [IMAGE AVAILABLE]

8. 5,849,877, Dec. 15, 1998, Antigen-binding sites of antibody molecules specific for cancer antigens; David B. Ring, 530/387.1; 435/69.7, 70.21, 326; 530/387.3, 387.7, 388.1, 388.2, 388.8 [IMAGE AVAILABLE]

9. 5,843,723, Dec. 1, 1998, Alphavirus vector constructs; Thomas W. Dubensky, Jr., et al., 435/69.3, 235.1, 320.1, 325 [IMAGE AVAILABLE]

10. 5,837,464, Nov. 17, 1998, Compositions and methods for determining anti-viral drug susceptibility and resistance and anti-viral drug screening; Daniel Capon, et al., 435/6, 320.1, 369 [IMAGE AVAILABLE]

11. 5,834,589, Nov. 10, 1998, Chimeric viral receptor polypeptides; Daniel Meruelo, et al., 530/350, 387.3, 388.3, 389.1, 826 [IMAGE AVAILABLE]

12. 5,830,458, Nov. 3, 1998, Method for destroying a diseased human cell; Harry E. Gruber, et al., 424/93.2, 93.21, 93.6 [IMAGE AVAILABLE]

13. 5,817,491, Oct. 6, 1998, VSV G pseusdotyped **retroviral** vectors; Jiing-Kuan Yee, et al., 435/456; 424/93.2; 435/320.1, 325, 366, 465 [IMAGE AVAILABLE]

14. 5,814,482, Sep. 29, 1998, Eukaryotic layered vector initiation systems; Thomas W. Dubensky, Jr., et al., 435/69.3, 320.1; 536/23.1, 24.1 [IMAGE AVAILABLE]

15. 5,811,267, Sep. 22, 1998, Isolated nucleic acid molecules encoding antigen binding sites of antibody molecules specific for cancer antigens; David B. Ring, 435/69.7, 70.21; 530/387.1, 387.3, 387.7, 388.8, 388.85; 536/23.1, 23.4 [IMAGE AVAILABLE]

16. 5,789,245, Aug. 4, 1998, Alphavirus structural protein expression cassettes; Thomas W. Dubensky, Jr., et al., 435/320.1, 69.1, 325; 536/23.72 [IMAGE AVAILABLE]

17. 5,766,945, Jun. 16, 1998, 10A1 **Retroviral packaging cells** and uses thereof; A. Dusty Miller, 435/235.1, 320.1, 325 [IMAGE AVAILABLE]

18. 5,750,396, May 12, 1998, Stable virus **packaging cell** lines; Yanping Yang, et al., 435/357, 320.1, 366; 536/23.72, 24.1 [IMAGE AVAILABLE]

19. 5,739,018, Apr. 14, 1998, **Packaging cell** lines for **pseudotyped retroviral** vectors; Atsushi Miyanohara, et al., 435/456, 320.1, 325, 463 [IMAGE AVAILABLE]

20. 5,731,182, Mar. 24, 1998, Non-mammalian DNA virus to express an exogenous gene in a mammalian cell; Frederick M. Boyce, 435/183, 69.1, 70.1, 320.1 [IMAGE AVAILABLE]

21. 5,723,333, Mar. 3, 1998, Human pancreatic cell lines: developments and uses; Fred Levine, et al., 435/325, 320.1, 377, 378 [IMAGE AVAILABLE]

22. 5,716,832, Feb. 10, 1998, **Packaging cells**; Jack R. Barber, et al., 435/235.1, 325 [IMAGE AVAILABLE]

23. 5,716,826, Feb. 10, 1998, Recombinant **retroviruses**; Harry E. Gruber, et al., 435/320.1; 536/23.5, 23.72 [IMAGE AVAILABLE]

24. 5,716,613, Feb. 10, 1998, Recombinant **retroviruses**; Harry E.

Guber, et al., 424/93.2; 435/320.1 [IMAGE AVAILABLE]

25. 5,693,508, Dec. 2, 1997, **Retroviral** expression vectors containing MoMLV/CMV-IE/HIV-TAR chimeric long terminal repeats; Lung-Ji Chang, 435/6, 69.1, 320.1, 456, 465; 536/24.1 [IMAGE AVAILABLE]

26. 5,691,177, Nov. 25, 1997, Recombinant **retroviruses** expressing a protein that converts a pro-drug into a cytotoxic agent; Harry E. Guber, et al., 435/456, 69.1, 372 [IMAGE AVAILABLE]

27. 5,681,746, Oct. 28, 1997, **Retroviral** delivery of full length factor VIII; Mordechai Bodner, et al., 435/350, 320.1, 366, 371; 536/23.5 [IMAGE AVAILABLE]

28. 5,670,354, Sep. 23, 1997, Use of VSV-G **pseudotyped** vectors for transfer of genes into embryos; Jane C. Burns, et al., 800/21; 435/320.1 [IMAGE AVAILABLE]

29. 5,665,577, Sep. 9, 1997, Vectors containing HIV packaging sequences, packaging defective HIV vectors, and uses thereof; Joseph G. Sodroski, et al., 435/456; 424/93.2; 435/236, 320.1, 325, 358, 362, 364, 367, 372, 457, 465 [IMAGE AVAILABLE]

30. 5,591,624, Jan. 7, 1997, **Retroviral packaging cell** lines; Jack R. Barber, et al., 435/366, 320.1, 369 [IMAGE AVAILABLE]

31. 5,512,421, Apr. 30, 1996, Generation, concentration and efficient transfer of VSV-G **pseudotyped retroviral** vectors; Jane C. Burns, et al., 435/320.1; 424/93.2; 435/239 [IMAGE AVAILABLE]

32. 5,470,730, Nov. 28, 1995, Method for producing T.sub.H -independent cytotoxic T lymphocytes; Phillip D. Greenberg, et al., 435/456; 424/93.21; 435/69.1, 69.52, 70.4, 252.3, 320.1 [IMAGE AVAILABLE]

33. 5,354,674, Oct. 11, 1994, Method of gene transfer using retrotransposons; Clague P. Hodgson, 435/6, 69.1, 235.1, 320.1, 463 [IMAGE AVAILABLE]

34. 4,861,719, Aug. 29, 1989, DNA constructs for **retrovirus packaging cell** lines; A. Dusty Miller, 435/236, 69.1, 91.42, 320.1, 357, 456, 457, 465, 948; 536/23.1, 24.1, 24.2 [IMAGE AVAILABLE]

=> d clms,1,7

US PAT NO: 5,888,502 [IMAGE AVAILABLE] L3: 1 of 34

CLAIMS:

CLMS(1)

We claim:

1. A pharmaceutical composition comprising:
a) a replication defective recombinant **retrovirus** which infects a human host cell, said recombinant **retrovirus** comprising a recombinant gene operable linked to a promoter, said gene encoding a protein which is not normally expressed in said host cell, and which converts a purine-based or pyrimidine-based drug to a compound that is toxic to said host cell, and
b) a pharmaceutically acceptable carrier.

CLMS(2)

2. The pharmaceutical composition of claim 1 wherein said purine-based

or pyrimidine-based drug is a prodrug with little or no cytotoxicity.

CLMS(3)

3. The pharmaceutical composition of claim 1 wherein said protein is guanine phosphoribosyl transferase.

CLMS(4)

4. The pharmaceutical composition of claim 1 wherein said protein causes phosphorylation, ribosylation, or phosphorylribosylation of said drug.

CLMS(5)

5. The pharmaceutical composition of claim 1 wherein expression of said protein by said recombinant **retrovirus** is regulated by the presence of an intracellular signal associated with the pathogenic state of an infectious or cancerous disease.

CLMS(6)

6. The pharmaceutical composition of claim 1 wherein said gene encoding said protein is of non-mammalian origin.

CLMS(7)

7. The pharmaceutical composition of claim 1, wherein said **retroviral** vector also comprises a gene encoding a cell surface marker.

CLMS(8)

8. The pharmaceutical composition of claim 2 wherein said protein is a nucleoside kinase.

CLMS(9)

9. The pharmaceutical composition according to claim 5 wherein said promoter is an event-specific promoter, and wherein expression of said protein by said promoter is regulated by said intracellular signal.

CLMS(10)

10. The pharmaceutical composition of claim 5, wherein said promoter is a tissue specific promoter.

CLMS(11)

11. The pharmaceutical composition of claim 8 wherein said nucleoside kinase is a thymidine kinase.

CLMS(12)

12. A pharmaceutical composition according to claim 9 wherein said disease is a cancerous disease and wherein said event-specific promoter is preferentially active in proliferating cells.

CLMS(13)

13. The phanmaceutical composition of claim 10, wherein said disease is a cancerous disease associated with a tumor and wherein the tissue origin of the tissue specific promoter corresponds to the tissue origin of the tumor.

CLMS(14)

14. The pharmaceutical composition of claim 11 wherein said thymidine kinase is of viral origin.

CLMS(15)

15. The pharmaceutical composition of claim 13, wherein said cancerous disease is a hepatocellular carcinoma and wherein said tissue-specific promoter is a liver specific promoter.

CLMS(16)

16. The pharmaceutical composition of claim 13, wherein said recombinant **retrovirus** further comprises a second promoter that is an event-specific promoter operably linked to the gene encoding said protein, and wherein the expression of said protein is regulated by said event-specific promoter and said tissue specific promoter.

CLMS(17)

17. The pharmaceutical composition of claim 14 wherein said thymidine kinase is herpes simplex thymidine kinase.

CLMS(18)

18. The pbanmaeeutical composition of claim 1 or 14, wherein said human host cell is a human peripheral blood lymphocyte.

CLMS(19)

19. A pharmaceutical composition comprising:
a) a producer cell which produces a replication defective recombinant **retrovirus** which infects a human host cell, said recombinant **retrovirus** comprising a recombinant gene operatively linked to a promoter, said gene encoding a protein which is not normally expressed in said human host cells and which converts a purine-based or pyrimidine-based drug to a compound that is toxic to said human host cell; and
b) a pharmaceutically acceptable carrier.

CLMS(20)

20. The pharmaceutical composition of claim 19, wherein said purine-based or pyrimidine-based drug is a prodrug with little or no cytotoxicity.

CLMS(21)

21. The pharmaceutical composition of claim 19, wherein said protein is a guaniine phosphloribosyl transferase.

CLMS(22)

22. The pharmaceutical composition of claim 19, wherein said protein causes phosphorylation, ribosylation or phosphorylribosylation of said drug.

CLMS(23)

23. The pharmaceutical composition of claim 19, wherein expression of said protein by said recombinant **retrovirus** is regulated by the presence of an intracellular signal associated with the pathogenic state of an infectious or cancerous disease.

CLMS(24)

24. The pharmaceutical composition of claim 19 wherein said gene encoding said protein is of non-mammalian origin.

CLMS(25)

25. The pharmiceutical composition of claim 19 wherein said producer cell is a human producler cell.

CLMS(26)

26. The phamiaceuttical composition of claim 19, wherein said **retroviral** vector also comprises a gene encoding a cell surface marker.

CLMS(27)

27. The pharmaceutical composition of claim 20, wherein said protein is a nucleoside kiniase.

CLMS(28)

28. The pharmaceutical composition of claim 23, wherein said promoter is an event-specific promoter, and wherein expression of said protein by said promoter is regulated by said intracellular signal.

CLMS(29)

29. The pharmaceutical composition of claim 23, wherein said promoter is a tissue-specific promoter.

CLMS(30)

30. The pharmaceutical composition of claim 27, wherein said nucleoside kinase is a thymidine kinase.

CLMS(31)

31. The pharmaceutical composition of claim 28, wherein said disease is a cancerous disease and said event-specific promoter is preferentially active in proliferating cells.

CLMS(32)

32. The pharmaceutical composition of claim 29, wherein said disease is a cancerous disease associated with production of a tumor and said tissue-specific promoter has tissue specificity that corresponds to the tissue origin of said tumor.

CLMS(33)

33. The pharmaceutical composition of claim 30, wherein said thymidine kinase is of viral origin.

CLMS(34)

34. The pharmaceutical composition of claim 32, wherein said cancerous disease is a hepatocellular carcinoma and wherein said tissue-specific promoter is a liver specific promoter.

CLMS(35)

35. The pharmaceutical composition of claim 32, wherein said recombinant **retroviris** further comprises a second promoter that is an event-specific promoter operably linked to the gene encoding said

protein, and wherein expression of said protein is regulated by said event-specific promot[redacted] and said tissue-specific promo[redacted].

CLMS(36)

36. The pharmaceutical composition of claim 33, wherein said thymidine kinase is a heroes simplex thymidine kinase.

CLMS(37)

37. A replication defective recombinant **retrovirus** which infects a human host cell, said recombinant **retrovirus** comprising a recombinant gene operably linked to a promoter, said gene encoding a protein which is not normally expressed in said host cell, and which converts a first agent in said host cell to a second agent that is toxic to said host cell.

CLMS(38)

38. The replication defective recombinant **retrovirus** of claim 37 wherein said first agent is a prodrug with little or no cytotoxicity.

CLMS(39)

39. The replication defective recombinant **retrovirus** of claim 37, wherein said protein catalyzes the metabolism of a purine-based or pyrimidine-based drug.

CLMS(40)

40. The replication defective recombinant **retrovirus** of claim 37, wherein expression of said protein by said recombinant virus is regulated by the presence of an intracellular signal associated with the pathogenic state of an infectious or cancerous disease.

CLMS(41)

41. The replication defective recombinant **retrovirus** of claim 37, wherein said gene encoding said protein is of non-mammalian origin.

CLMS(42)

42. The replication defective recombinant **retrovirus** of claim 37 further comprising a gene encoding a cell surface marker.

CLMS(43)

43. The replication defective recombinant **retrovirus** of claim 38, wherein said protein is a nucleoside kinase.

CLMS(44)

44. The replication defective recombinant **retrovirus** of claim 39, wherein said protein is guanine phosphoribosyl transferase.

CLMS(45)

45. The replication defective recombinant **retrovirus** of claim 39, wherein said protein causes phosphorylation, ribosylation, or phosphoribosylation of said drug.

CLMS(46)

46. The replication defective recombinant **retrovirus** of claim 37 or 39, wherein said human host cell is a human peripheral blood lymphocyte.

CLMS(47)

47. The replication defective recombinant **retrovirus** of claim 40, wherein said promoter is an event-specific promoter, and wherein expression of said protein by said promoter is regulated by said intracellular signal.

CLMS(48)

48. The replication defective recombinant **retrovirus** of claim 40, wherein said promoter is a tissue specific promoter.

CLMS(49)

49. The replication defective recombinant **retrovirus** of claim 43, wherein said nucleoside kinase is a thymidine kinase.

CLMS(50)

50. The replication defective recombinant **retrovirus** according to claim 47, wherein said disease is a cancerous disease and wherein said event-specific promoter is preferentially active in proliferating cells.

CLMS(51)

51. The replication defective recombinant **retrovirus** of claim 48, wherein said disease is a cancerous disease associated with a tumor and wherein the tissue origin of the tissue specific promoter corresponds to the tissue origin of the tumor.

CLMS(52)

52. The replication defective recombinant **retrovirus** of claim 49, wherein said thymidine kinase is herpes simplex thymidine kinase.

CLMS(53)

53. The replication defective recombinant **retrovirus** of claim 51, wherein said cancerous disease is hepatocellular carcinoma and wherein said tissue-specific promoter is a liver-specific promoter.

CLMS(54)

54. The replication defective recombinant **retrovirus** of claim 51, wherein said recombinant **retrovirus** further comprises a second promoter that is an evenit-specific promoter operably linked to the gene encoding said protein, and wherein the expression of said protein is regulated by said event-specific promoter and said tissue specific promoter.

CLMS(55)

55. A producer cell which produces a replication defective recombinant **retrovirus** which infects a human host cell, said recombinant **retrovirus** comprising a recombinant gene operably linked to a promoter, said gene encoding a protein not normally expressed in said human cell, and which converts an agent in said human host cell to a second agent that is toxic to said human host cell.

CLMS(56)

56. The producer cell of claim 55, wherein said first agent is a prodrug with little or no cytotoxicity.

CLMS(57)

57. The producer cell of claim 55, wherein said protein catalyzes the metabolism of a purine-based or pyrimidine-based dnig.

CLMS(58)

58. The producer cell of claim 55, wherein expression of said protein by said recombinant **retrovirus** is regulated by the presence of an intracellular signal associated with the pathogenic state of an infectious cancerous disease.

CLMS(59)

59. The producer cell of claim 55, wherein said gene encoding protein is of non-mammalian origin.

CLMS(60)

60. The producer cell of claim 55, wherein the producer cell is a human producer cell.

CLMS(61)

61. The producer cell of claim 55, wherein said recombinant **retrovirus** further comprises a gene encoding a cell surface marker.

CLMS(62)

62. The producer cell of claim 56, wherein said protein is a nucleoside kinase.

CLMS(63)

63. The producer cell of claim 57, wherein said protein is a guanine phosphoribosyl transferase.

CLMS(64)

64. The producer cell of claim 57, wherein said protein causes phosphorylation, ribosylation or phosphorylribosylation of said drug.

CLMS(65)

65. The producer cell of claim 58, wherein said promoter is an event-specific promoter, and wherein expression of said protein by said promoter is regulated by said intracellular signal.

CLMS(66)

66. The producer cell of claim 58, wherein said promoter is a tissue-specific promoter.

CLMS(67)

67. The producer cell of claim 62, wherein said nucleoside kinase is a thymidine kinase.

CLMS(68)

68. The producer cell of claim 65, wherein said disease is a cancerous disease and said event-specific promoter is preferentially active in proliferating cells.

CLMS(69)

69. The producer cell of claim 66, wherein said disease is a cancerous disease associated with production of a tumor and said tissue-specific promoter has tissue specificity that corresponds to the tissue origin of said tumor.

CLMS(70)

70. The producer cell of claim 67, wherein said thymidine kinase is a herpes simplex thymidine kinase.

CLMS(71)

71. The producer cell of claim 69, wherein said cancerous disease is a hepatocelluilar carcinoma and wherein said tissue-specific promoter is a liver specific promoter.

CLMS(72)

72. The producer cell of claiim 69, wherein said recombinant **retrovirus** further comprises a second promoter that is an event-specific promoter operably linked to the gene encoding said protein, and wherein expression of said protein is regulated by said event-specific promoter and said tissue-specific promoter.

US PAT NO: 5,851,529 [IMAGE AVAILABLE] L3: 7 of 34

CLAIMS:

CLMS(1)

We claim:

1. A method of stimulating a cell-mediated immune response to a viral or cancer antigen in a human, comprising infecting susceptible target cells with a replication defective recombinant **retrovirus** construct directing the expression of said viral or cancer antigen or mutated form thereof in said infected target cells, wherein said viral antigen is from a virus that is pathogenic to humans, and wherein said antigen or mutated form thereof elicits a cell-mediated immune response directed to said viral or cancer antigen or mutated form thereof in said human.

CLMS(2)

2. The method of claim 1 wherein said expressed viral or cancer antigen or mutated form thereof elicits an HLA class I-restricted immune response.

CLMS(3)

3. The method of claim 1 wherein said expressed viral or cancer antigen or mutated form thereof elicits an HLA class II-restricted immune response.

CLMS(4)

4. The method of claim 1 wherein said expressed viral or cancer antigen or mutated form thereof elicits both an HLA class I-restricted response and an HLA class II-restricted immune response.

CLMS(5)

5. The method of claim 1 wherein said cancer antigen is selected from the group consisting of a cervical carcinoma antigen, a leukemia antigen, a prostate cancer antigen, a colon cancer antigen, and a melanoma

antigen.

CLMS(6)

6. The method of claim 1 wherein said cancer antigen is selected from the group consisting of an HPV antigen, an HTLV I antigen, prostate specific antigen, mutated p53 protein, and GD2 antigen.

CLMS(7)

7. The method of claim 1 wherein said expressed viral antigen is an HIV protein or mutated form thereof.

CLMS(8)

8. The method of claim 7 wherein said HIV protein is an HIV envelope protein.

CLMS(9)

9. A method of stimulating a cell-mediated immune response to a viral or cancer antigen in a human, comprising:
infecting cells isolated from a human with a recombinant **retrovirus** construct directing the expression of said viral or cancer antigen or mutated form thereof, wherein said viral antigen is from a virus which is pathogenic to humans, and wherein said antigen or mutated form thereof stimulates a cell mediated immune response directed to said viral or cancer antigen or mutated form thereof in a human; and
administering said infected cells to a human, thereby stimulating a cell mediated immune response directed to said viral or cancer antigen or mutated form thereof within said human.

CLMS(10)

10. The method of claim 9 wherein said expressed viral or cancer antigen or mutated form thereof elicits an HLA class I-restricted immune response.

CLMS(11)

11. The method of claim 9 wherein said expressed viral or cancer antigen or mutated form thereof elicits an HLA class II-restricted immune response.

CLMS(12)

12. The method of claim 9 wherein said expressed viral or cancer antigen or mutated form thereof elicits both an HLA class I-restricted response and an HLA class II-restricted immune response.

CLMS(13)

13. The method of claim 9 wherein said cancer antigen is selected from the group consisting of a cervical carcinoma antigen, a leukemia antigen, a prostate cancer antigen, a colon cancer antigen, and a melanoma antigen.

CLMS(14)

14. The method of claim 9 wherein said cancer antigen is selected from the group consisting of an HPV antigen, an HTLV I antigen, prostate specific antigen, mutated p53 protein, and GD 2 antigen.

CLMS(15)

15. The method of claim 9 wherein said expressed viral antigen is an HIV protein or mutated form thereof.

CLMS(16)

16. The method of claim 15 wherein said HIV protein is an HIV envelope protein.